Cardiol Ther (2023) 12:557–570
https://doi.org/10.1007/s40119-023-00338-1

GUIDELINES

Cardiovascular Compatibility of Proton Pump Inhibitors: Practice Recommendations

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Received: August 24, 2023 / Accepted: October 18, 2023 / Published online: November 10, 2023

ABSTRACT

This manuscript aims to critically evaluate the current evidence regarding adverse cardiovascular effects associated with proton pump inhibitors (PPIs) in patients with coronary artery disease (CAD). It also provides guidance for the selection of the most appropriate PPI within the context of cardiovascular polypharmacy and emphasizes the importance of establishing consensus among clinicians on the need to prescribe PPIs with limited cytochrome P450 (CYP450) enzyme inhibition to reduce the risk of drug interactions. PPIs are among the most widely used drugs for the treatment of gastroesophageal reflux disease (GERD) and the prevention of gastrointestinal (GI) bleeding. The manuscript reports the proceedings from the first practice recommendations meeting on the cardiovascular compatibility of PPIs in an Indian setting. A panel of eight Indian experts in cardiology and gastroenterology reviewed 14 consensus statements. Available literature was searched and summarized, and after multiple rounds of review, consensus was achieved for these statements. Based on the available evidence, the consensus panel highlights that a PPI with minimal drug–drug interaction (DDI) is recommended, especially in patients requiring clopidogrel or polypharmacy. Rabeprazole appears to be a good option in cases where co-prescription is indicated, owing to its optimal acid suppression and minimal drug interaction profile.

Keywords: Proton pump inhibitors; Cardiovascular risk; Polypharmacy; CYP450 enzyme; Clopidogrel; Rabeprazole

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Key Summary Points

Co-administration of proton pump inhibitors (PPIs) with drugs that have high affinity for either CYP2C19 or CYP3A4 (cytochrome P450 enzyme family) may cause a clinically relevant drug–drug interaction (DDI).

Rabeprazole with low affinity for a range of CYP isoenzymes or involvement of additional elimination processes exhibits a minor propensity for DDIs compared to other PPIs.

The risk of major adverse cardiovascular events (MACE) was similarly higher with omeprazole, esomeprazole, lansoprazole, and pantoprazole but not with rabeprazole when given along with clopidogrel.

Considering the optimal acid suppression and minimal drug interaction profile of rabeprazole, it seems to be a good option in cases where co-prescription with dual antiplatelet therapy (DAPT) is indicated.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally. India accounts for one-fifth of the CVD deaths worldwide, especially among youth. India's CVD prevalence increased from 25.7 million in 1990 to 54.5 million in 2016 [1]. One study reports that the prevalence of CVD in 1960 in urban India was 2.0%, and by 2013 it had increased sevenfold to ≈14.0%. The rural prevalence more than quadrupled from 1.7% in 1970 to 7.4% in 2013 [2].

Antithrombotic therapy with antiplatelet drugs and oral anticoagulants is the standard of care in patients with CVD. Patients undergoing antithrombotic therapy are at risk of gastrointestinal (GI) bleeding. Proton pump inhibitors (PPIs) are co-prescribed with antithrombotic agents for gastroprotection and reduce the risk of GI bleeding. PPIs are potential inhibitors of hepatic cytochrome P450 (CYP450) enzymes, which may result in clinically significant drug interactions. Therefore, it is imperative that effective strategies are used as well as regular monitoring in order to improve patient compliance [3].

METHODS

A survey was conducted to address several issues concerning PPIs. The objective of this survey was to appraise the current evidence on adverse cardiovascular (CV) effects from PPIs in patients with CVD and provide guidance on selecting a PPI with weak CYP450 enzyme inhibition. An initial list of 14 statements along with the available literature was generated and circulated among the eight key opinion leaders (KOLs) in the field (six cardiologists/two gastroenterologists). After reviewing the statements, the KOLs voted on the statements by email. The options given for each statement were as follows: (a) strongly agree, (b) agree with some reservation, and (c) disagree. Consensus on a statement was considered achieved when 80.0% or more of the KOLs chose to "strongly agree" or "agree with some reservation". A statement was considered refuted when 80.0% or more of the KOLs chose to "disagree". The final document was again circulated among the panelists for their approval on the practice recommendations. This document provides guidance for doctors in India in choosing a PPI with fewer drug–drug interactions (DDI) when prescribing to patients with CVD, thereby reducing the risk of adverse CV effects and drug interactions. This article does not contain any new studies with human participants or animals performed by any of the authors.

PRACTICE RECOMMENDATION STATEMENTS

Statement 1: There Is a Strong Association Between Cardiac and GI Disorders

Review of the Literature

There is a clear link between heart disease and GI problems (Fig. 1). Most patients attribute

their coronary artery disease (CAD) symptoms to "gas" and acidity, which results in delayed diagnosis and poor outcomes of CAD.

Gastroesophageal reflux disease (GERD) is associated not only with non-cardiac chest pain episodes, but also with increased incidence of ischemic events in patients with CVD and refractory chest pain [4]. In patients with CAD undergoing percutaneous coronary intervention (PCI), antithrombotic therapy is used to minimize the risk of stent thrombosis and recurrent CV events [5]. Antithrombotic therapy is associated with high risk of GI bleeding. Increased GI bleeding is associated with an increased risk of CV events and mortality, and prolonged hospitalization [6]. Polypharmacy with drugs used to manage CVD can cause upper GI symptoms. Some drugs used to treat upper GI symptoms may increase CVD risk either directly or through drug–drug interactions. Therefore, recognizing patients with both CVD and upper GI conditions is an important step in the clinical care setting [7]. PPI use for an extended period of time may suppress dimethylarginine dimethylaminohydrolase (DDAH) activity. This leads to increased asymmetrical dimethyl arginine (ADMA) levels which inhibit nitric oxide (NO) synthesis and increase the risk of CVD [8].

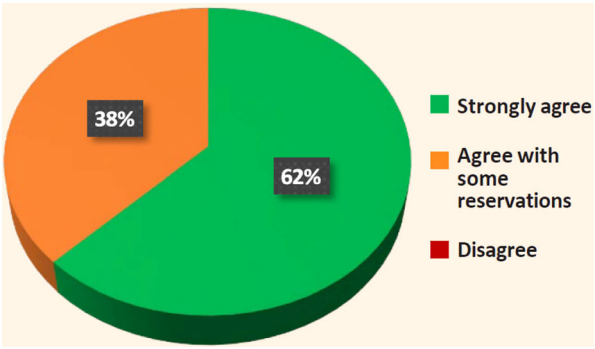

Fig. 1 Association between cardiac and GI disorders. This figure illustrates the strong association between cardiac and GI disorders. The consensus level among participants was 100%, with 62% strongly agreeing and 38% agreeing with some reservations. *GI* gastrointestinal

Statement 2: Increased GI Bleeding Increases CV Events, Mortality, and Prolonged Hospitalization

Review of the Literature

Acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), and anticoagulant or antiplatelet drugs are all known to cause GI bleeding in patients admitted to the cardiology department [9]. Not only does this cause prolonged hospitalization but also increases the risk of CV events and mortality (Fig. 2) [10]. Post-procedural bleeding episodes were linked to an elevated risk of in-hospital mortality in a large registry of PCI patients, with an estimated 12.1% of fatalities due to bleeding complications [11]. GI bleeding is a catastrophic condition in the setting of acute coronary syndrome (ACS). It is associated with increased rates of mortality, nonfatal MI, stent thrombosis, and prolonged hospitalization. The duration of hospitalization is twice as long in patients with GI bleeding as in those without GI bleeding [12]. GI bleeding adversely affects CAD outcomes in many ways. One of them which is not often discussed is that secondary to bleeding as a compensatory mechanism, coagulation factors become more proactive resulting in more thrombotic events [6]. According to

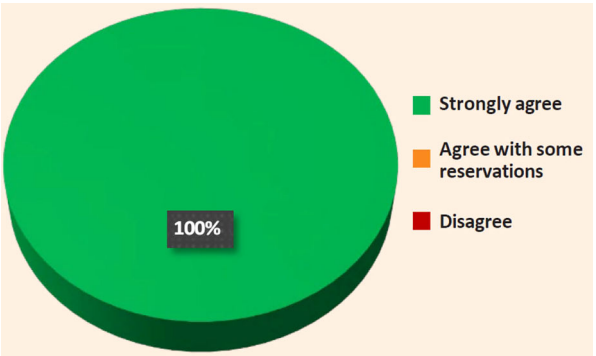

Fig. 2 Consequences of increased GI bleeding with respect to cardiovascular events, mortality, and hospitalization. The figure illustrates the association between increased GI bleeding and its consequences, including cardiovascular events, mortality, and prolonged hospitalization. The consensus level reached 100% agreement. *GI* gastrointestinal

international societal guidelines, patients with a history of upper GI bleeding should take PPIs to minimize GI bleeding. PPIs are helpful for patients who require antiplatelet medication and have associated risk factors for GI bleeding [13].

Statement 3: There Is an Immense Burden of Polypharmacy and Significant DDI in Cardiac Patients

Review of Literature

Patients with CVD need to be prescribed two or more essential drugs [14]. These drugs together can cause drug interactions (Fig. 3). Cardiovascular pharmaceuticals make up 48.0% of all prescribed medications, which is quite high [15]. A study which included 466 patients showed that 26.7% of participants met the criteria of polypharmacy. Polypharmacy, while sometimes unavoidable, is not always effective or safe. It can have a high risk of negative side effects [16]. The most severe medication interactions were identified to be aspirin + clopidogrel (46.8%) and omeprazole + clopidogrel (32.4%) in the same prescription. It has been shown that combining a PPI with clopidogrel in a single prescription can result in serious medication interactions [15]. Despite these interactions, PPIs have been suggested as a way to reduce the risk of GI bleeding after dual antiplatelet therapy (DAPT). The patient's GI risk must be assessed, and PPIs with the least interaction with clopidogrel must be chosen carefully [15]. Therefore, clinicians should differentiate between appropriate and inappropriate polypharmacy and strive to reduce inappropriate polypharmacy and severe DDI [16].

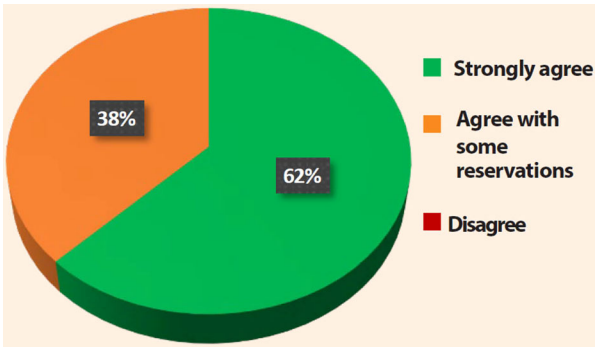

Fig. 3 Polypharmacy and DDI burden in cardiac patients. The figure highlights a significant consensus level (100%) regarding the burden of polypharmacy and DDI in cardiac patients, with 62% strongly agreeing and 38% agreeing with some reservations. *DDI* drug–drug interaction

Statement 4: The Most Prescribed Single Drug in Cardiac Patients Is Aspirin and the Fixed-Dose Combination Is Aspirin + Clopidogrel

Review of the Literature

Antiplatelet agents (67.7%) dominate the cardiology outpatient department (OPD) prescribing trend and are projected to overtake anticholesterol medications as the top seller. The most prescribed single drug was aspirin (59.9%) [17] (Fig. 4). Aspirin and clopidogrel were the most widely recommended antiplatelet drugs for the treatment of CVD [18].

The combination of aspirin and clopidogrel is essential in the treatment of CVD because the drugs minimize the risk of additional clot formation and help to improve survival rates [18]. Platelet activation is inhibited by aspirin and clopidogrel through complementary but distinct mechanisms. Both these antiplatelet drugs have a substantial protective impact against unfavorable vascular events, but the combination of the two agents has an even stronger antiplatelet effect, resulting in superior antithrombotic protection in CVD and peripheral arterial disease (PAD) [19].

Statement 5: PPIs Are Recommended for Gastroprotection in Patients with CAD Receiving Antithrombotic Therapy

Review of the Literature

DAPT with aspirin and a P2Y12 inhibitor improves CV outcomes in patients with acute coronary syndrome (ACS) and is recommended by guidelines for one year following initial hospitalization [20]. Clopidogrel has been linked to an elevated risk of upper GI bleeding and ulcers. To reduce the risk of GI hemorrhage, PPIs are recommended. In CAD, PPIs have been demonstrated to minimize dyspepsia caused by

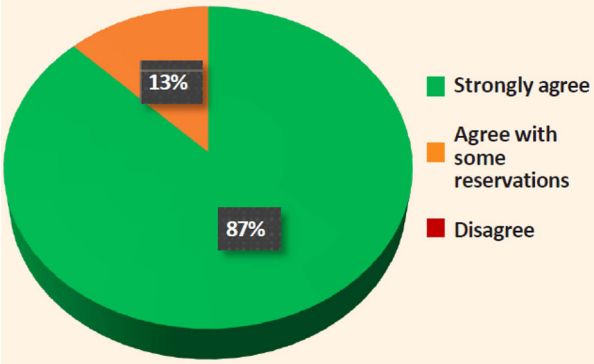

Fig. 4 Aspirin and aspirin + clopidogrel—common medications in cardiac patients. The figure summarizes the common medications used in cardiac patient care, including aspirin as the single drug and the combination of aspirin + clopidogrel. The consensus level was 100%, with 87% strongly agreeing and 13% agreeing with some reservations

DAPT and to achieve a clinically significant reduction in GI bleeding [20]. According to a systematic assessment of 18 randomized controlled trials (RCTs) involving over 10,000 patients, PPIs reduced peptic ulcer bleeding by almost 80.0% when compared to controls [21]. Mistry et al. reported that gastroprotection in the form of PPIs is required for patients on DAPT and/or with a history of GI bleeding [22]. A meta-analysis conducted by Almufleh et al. reported that PPIs are superior to H2 receptor antagonists (H2RAs) for gastroprotection in patients on DAPT [23]. These data suggest that PPI therapy has a definite gastroprotective role in patients with CVD (Fig. 5) who are prescribed antiplatelets, but the usage should be in accordance with the recommended dose and treatment period [24].

Statement 6: PPIs Affect the Efficacy of DAPT in Cardiac Patients

Review of the Literature

Clopidogrel has been used as an antiplatelet drug in most studies for DAPT. Concurrent use of clopidogrel and PPIs may reduce the overall efficacy of clopidogrel (Fig. 6) due to the DDIs between some PPIs and clopidogrel, metabolized via the same CYP450 liver enzymes [25]. In 2009, the Food and Drug Administration (FDA) issued a warning about concomitant use of clopidogrel and certain PPIs, as the antiplatelet action of clopidogrel may be limited by PPIs like omeprazole and esomeprazole [26]. Yamane et al. reported that omeprazole lowered clopidogrel's antiplatelet action more than rabeprazole [26]. Among individual PPIs, only omeprazole was significantly linked with an increased risk of hospitalization for ACS [27]. The results of a meta-analysis exploring the risk of major adverse cardiovascular events (MACE) following combined use of clopidogrel and PPIs in patients with CAD showed that the increased risk of MACE was similarly high with omeprazole, esomeprazole, lansoprazole, and pantoprazole but not with rabeprazole [28]. A study by Parri et al. showed that pantoprazole increased the adenosine diphosphate-induced maximal aggregation (ADP-MA) in patients with ST-elevation myocardial infarction (STEMI) treated with DAPT. It significantly interferes with the antiplatelet effects of clopidogrel. Therefore, pantoprazole is not a safer choice for patients on DAPT [29]. The available evidence suggests that there is an increased risk of MACE in patients with concomitant use of clopidogrel and PPIs, but it is different for different PPIs [30]. In the last few years, newer antiplatelet agents (ticagrelor/prasugrel) have been used as alternatives to clopidogrel after coronary intervention. There are no known drug interactions with prasugrel and ticagrelor

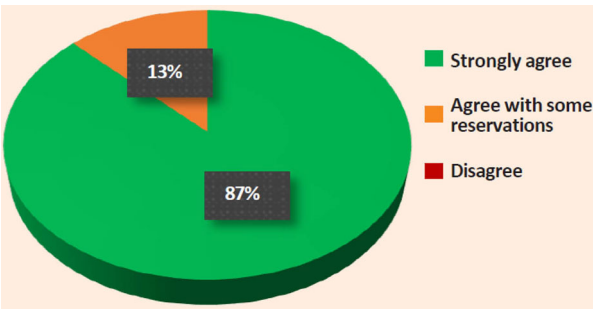

Fig. 5 PPI recommendations for gastroprotection in patients with CAD. The figure highlights the recommendations for PPIs in providing gastroprotection for patients with CAD, with a consensus level of 100%, including 87% strongly agreeing and 13% agreeing with some reservations. *CAD* coronary artery disease, *PPI* proton pump inhibitor

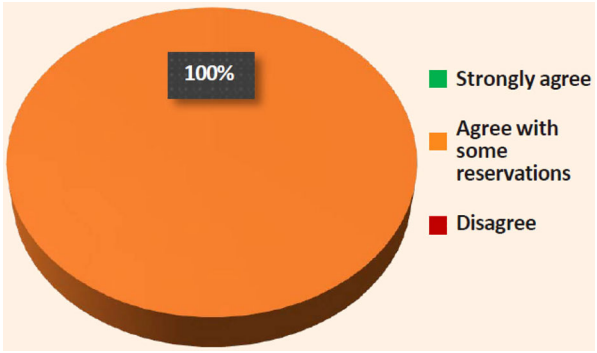

Fig. 6 Influence of PPIs on DAPT effectiveness in cardiac patients. The figure highlights how PPIs influence the effectiveness of DAPT in cardiac patients, with a consensus level of 100%, agreeing with some reservations. *PPI* proton pump inhibitor, *DAPT* dual antiplatelet therapy

that would significantly hinder their antiplatelet effects [31].

Statement 7: PPIs and Antiplatelet Drugs Share a Common Cytochrome P450 Metabolic Pathway

Review of the Literature

Most drugs undergo oxidation by one or more CYP isoenzymes, which is the most important metabolic pathway. The activity of CYP isoenzymes may also be required for the conversion of a prodrug into a clinically useful active metabolite [32]. Several PPIs and antiplatelet agents are metabolized by the hepatic cytochrome P450 enzymes (mainly CYP 2C19 and 3A4) (Fig. 7) implying the possibility of DDIs. Clopidogrel is a prodrug and is converted into active form through cytochrome-P450 enzymes dependent metabolism, however, PPIs have the potential to compete for the active site of CYP2C19, the enzyme responsible for converting clopidogrel into its active form. Clopidogrel's antiplatelet activity is thought to be inhibited by competitive inhibition, putting patients taking both these drugs at a higher risk of CV events than clopidogrel-treated individuals who do not take PPIs [33]. All PPIs except for rabeprazole are extensively metabolized by and competitively inhibit CYP2C19 and CYP3A4 (Fig. 8). Omeprazole, pantoprazole, and lansoprazole appear to be the strongest inhibitors of these enzymes, whereas the inhibitory potency of rabeprazole was lower than that of the other PPIs [34]. Ticagrelor and prasugrel are metabolized predominantly by CYP enzymes other than CYP2C19 [35, 36]. Clopidogrel is hydrolyzed by esterases to an inactive carboxylic acid metabolite, and the remaining drug is oxidized to active thiol metabolite in a two-step process by hepatic P450 cytochromes (CYP3A4/5 and CYP2C19 have a greater role). Multiple pharmacodynamic drug interactions can influence active thiol metabolite levels [32].

Statement 8: Not All PPIs Are Metabolized Predominantly by the CYP450 Pathway

Review of the Literature

PPIs are largely eliminated in the liver by the CYP2C19 enzyme, with CYP3A4 playing a smaller role. The extent to which PPIs are metabolized by CYP2C19 varies, resulting in variations in their pharmacokinetic and pharmacodynamic properties, which has an impact on their efficacy (Fig. 9). CYP2C19 is responsible for more than 80.0% of the metabolism of omeprazole, lansoprazole, and pantoprazole [37].

Rabeprazole undergoes extensive hepatic metabolism, predominantly nonenzymatic reduction to thioether and to a lesser extent via CYP2C19 and CYP3A4. As a result, rabeprazole

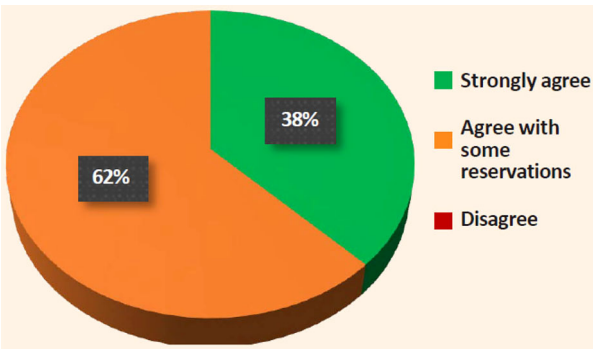

Fig. 7 PPIs and antiplatelet drugs share a common cytochrome P450 metabolic pathway. This figure highlights the common cytochrome P450 metabolic pathway shared by PPIs and antiplatelet drugs, with a consensus level of 100%, including 38% strongly agreeing and 62% agreeing with some reservations. *PPI* proton pump inhibitor

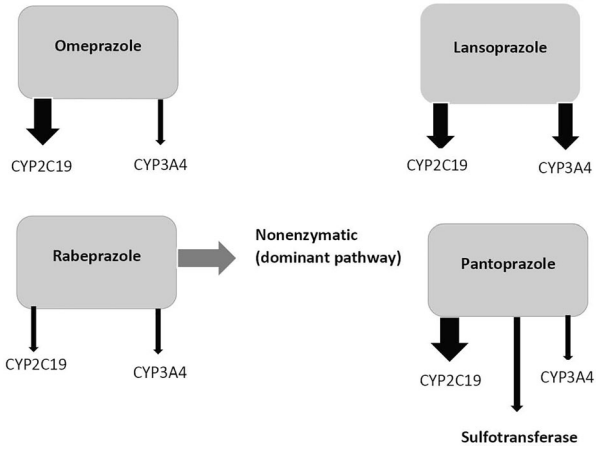

Fig. 8 Major metabolic pathways for the PPIs and the CYP 450 enzymes involved. The contribution of each isoenzyme is represented by the thickness of the arrow (thick arrows indicate the dominant pathway; thin arrows indicate the non-dominant pathway). *PPI* proton pump inhibitor. Note: Adapted from Sugimoto et al. Proton pump inhibitor therapy before and after endoscopic submucosal dissection: A review. *Diagn Ther Endosc*. 2012; 791873. https://doi.org/10.1155/2012/791873. Copyright © 2012 Sugimoto et al. This is an open access article, licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0)

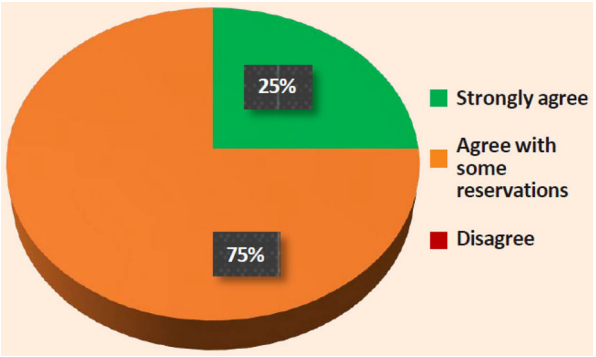

Fig. 9 Not all PPIs are metabolized predominantly by the CYP450 pathway. The figure illustrates that not all PPIs are predominantly metabolized by the CYP450 pathway. The consensus level among participants was 100%, with 25% strongly agreeing and 75% agreeing with some reservations. *PPI* proton pump inhibitor

may be less affected by CYP2C19 genetic variation or medication interactions than other PPIs. Rabeprazole has a much smaller difference in area under the curve (AUC) between the two groups (extensive metabolizers [EM]; poor metabolizers [PM]) compared to other PPIs. The acid suppression effect of PPIs is dependent on the plasma levels of the parent compound, and the AUC of PPIs is related to the degree of acid inhibition. As a result, it stands to reason that changes in CYP2C19 metabolic activity, which are influenced by genetic variability, would alter PPI efficacy [37]. Differences in hepatic metabolism caused by the CYP2C19 genetic polymorphism may contribute to inter-patient heterogeneity in PPI plasma levels, acid suppression, and clinical effectiveness [38]. Omeprazole alters the absorption, metabolism, and/or excretion of a wide range of drugs, including bismuth, caffeine, carbamazepine, diazepam, digoxin, mephenytoin, methotrexate, nifedipine, phenytoin, and warfarin. Ketoconazole inhibits the metabolism of omeprazole to omeprazole sulfone in both CYP2C19 poor and extensive metabolizers. Drug interaction studies with rabeprazole reveal no such significant drug interactions with drugs like theophylline, phenytoin, warfarin, or diazepam [38].

Statement 9: A PPI with Minimal DDI Is Recommended, Especially in Patients Requiring Clopidogrel or Polypharmacy

Review of the Literature

Clopidogrel, a widely used P2Y12 inhibitor, is associated with an increased risk of upper GI bleeding and ulcer, and to mitigate this risk of GI hemorrhage, PPIs are recommended for providing gastroprotection by maintaining the intragastric milieu. Considering the pharmacological interaction between clopidogrel and some PPIs on the basis of mutual CYP450-dependent metabolism, PPIs may inhibit the conversion of clopidogrel to its active metabolite and thereby diminish its clinical efficacy. This has led to growing debate about polypharmacy, arguing that it is sometimes inevitable but not always efficacious [20].

Both clopidogrel and PPIs are extensively metabolized by the CYP2C19 isoenzyme; therefore, PPIs with high affinity towards CYP2C19 should be avoided to minimize the

interaction between this combination (PPI and clopidogrel) or with other drugs in the prescription that are metabolized by the same pathway, and PPIs with the lowest affinity towards CYP2C19 is recommended (Fig. 10). Of note, numerous studies have demonstrated that PPI-induced risk reduction in GI bleeding clearly outweighs the risk of adverse CV events; therefore, in patients at high risk of GI bleeding, PPIs with less CYP2C19-inhibiting potential are recommended [39].

Statement 10: Rabeprazole Does Not Interact with Clopidogrel to the Same Extent as Other PPIs

Review of the Literature

The efficacy, availability, and lower side effect profile of PPIs make them suitable candidates to be prescribed along with clopidogrel to alleviate the risk of GI bleeding in the susceptible population. Of note, different PPIs are associated with different CV risks.

As noted by Sarnaik et al. [40], the increasing order of interaction strength of different PPIs, from lowest to highest affinity towards CYP2C19, is as follows: rabeprazole, pantoprazole, lansoprazole, esomeprazole, and omeprazole (Fig. 11).

Further, the results of a recent meta-analysis exploring the risk of MACE following the combined use of clopidogrel and PPIs in patients with CAD showed that the risk of MACE in the rabeprazole group was negligible as compared to other PPIs [28].

Statement 11: Rabeprazole Prevents Recurrence of Peptic Ulcers in Patients on Low-Dose Aspirin Treatment

Review of the Literature

A study conducted by Sugimoto et al. [41] concluded that rabeprazole remarkably inhibits acid secretion regardless of CYP2C19 genotypes and reduces the incidence of aspirin-related mucosal injury.

Further, these results were substantiated by Uotani et al. [42], who reported that rabeprazole provides protection against low-dose aspirin (LDA)-induced mucosal injury, and that too without interfering with clopidogrel's action (Fig. 12).

Later on, a study was planned to assess the long-term (76 weeks) efficacy and safety profile of rabeprazole in preventing peptic ulcer recurrence in patients on LDA therapy. In this study, 151 subjects in the rabeprazole 10-mg group and 150 subjects in the rabeprazole 5-mg group (5/10 mg is the standard dose in Japan, whereas the approved dosage of rabeprazole in India is 10/20 mg) were analyzed. The results of the study revealed that the cumulative peptic ulcer

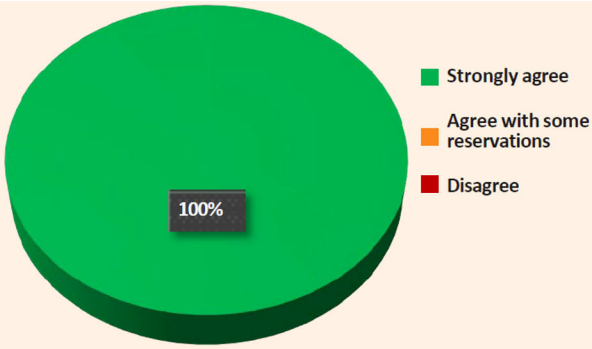

Fig. 10 PPIs with minimal DDI should be preferred. The figure shows that a PPI with minimal DDI should be preferred, especially in patients requiring clopidogrel or polypharmacy. The consensus level among participants was 100%, with 100% strongly agreeing. *PPI* proton pump inhibitor, *DDI* drug–drug interaction

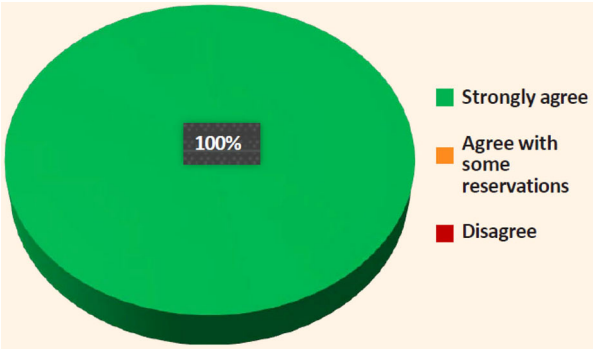

Fig. 11 Rabeprazole does not interact with clopidogrel to the same extent as other PPIs. The figure illustrates that rabeprazole does not interact with clopidogrel to the same extent as other PPIs. The consensus level among participants was 100%, with 100% strongly agreeing. *PPIs* proton pump inhibitors

recurrence rates were as low as 2.2% in the 10-mg group and 3.7% in the 5-mg group, and no bleeding ulcers or clinically significant CV events were reported; also, both doses of rabeprazole were well tolerated [43].

Statement 12: No Increased Risk of MACE Is Observed When Rabeprazole Is Given in Cardiac Patients Receiving DAPT (Clopidogrel and Aspirin)

Review of the Literature

A large body of evidence indicates that a PPI such as rabeprazole, a weak inhibitor of CYP2C19, has the lowest propensity for clinically relevant drug interactions in comparison to other PPIs, in cardiac patients receiving clopidogrel and aspirin [44].

A study was conducted to determine the incidence of GI bleeding and MACE in 199 patients in the control group (treated with DAPT alone) and 103 patients in the rabeprazole group (treated with rabeprazole plus DAPT). Researchers reported no significant increase in the incidence of MACE in the rabeprazole group (n = 103) versus the control group (n = 188). MACE was reported in 8.7% of patients in the rabeprazole group and 6.9% in the control group, cardiac death was 1.1% in the control group as compared to 0 in the rabeprazole group, ACS was reported in 1.0% of patients in the rabeprazole group and 0 in the control group, and stent thrombosis was reported in 1.0% and 0.5% of patients in the rabeprazole and control groups, respectively. Thus, the use of rabeprazole did not increase the incidence of MACE, when administered to cardiac patients receiving DAPT [45] (Fig. 13).

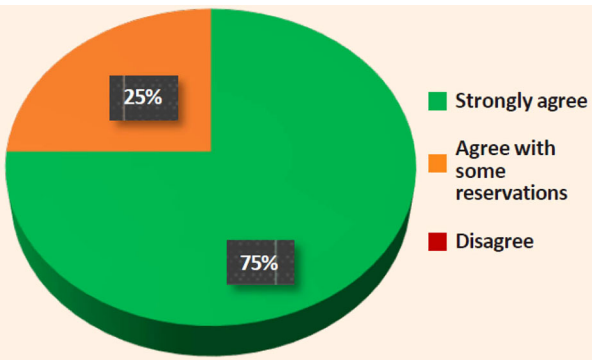

Fig. 12 Rabeprazole prevents recurrence of peptic ulcers in patients on low-dose aspirin treatment. The figure illustrates that rabeprazole prevents recurrence of peptic ulcers in patients on low-dose aspirin treatment. The consensus level among participants was 100%, with 75% strongly agreeing and 25% agreeing with some reservations

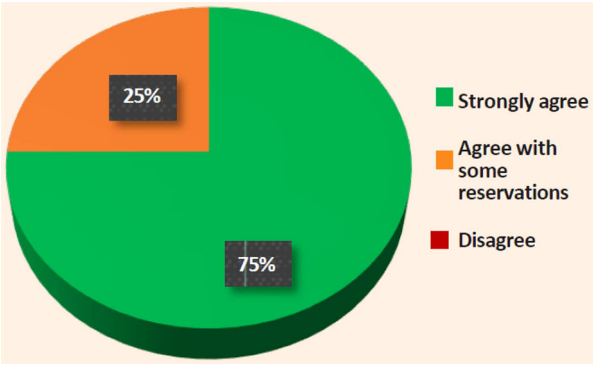

Fig. 13 Risk of MACE is not increased when rabeprazole is administered to cardiac patients receiving clopidogrel and aspirin. The figure shows that the risk of MACE is not increased when rabeprazole is administered to cardiac patients receiving DAPT (clopidogrel and aspirin). The consensus level among participants was 100%, with 75% strongly agreeing and 25% agreeing with some reservations. *MACE* major adverse cardiovascular events, *DAPT* dual antiplatelet therapy

Statement 13: When Concomitant Use of a PPI and Clopidogrel Is Warranted, Rabeprazole May Be Safer Than Other PPIs in Terms of MACE Risk

Review of the Literature

Data obtained from various studies show a similar increased risk of MACE with omeprazole, esomeprazole, lansoprazole, and pantoprazole but not with rabeprazole, in patients receiving the clopidogrel–PPI combination. The odds ratio for the risk of MACE was lowest with rabeprazole (1.03) relative to pantoprazole, omeprazole, lansoprazole, and esomeprazole (Table 1) [28].

A 2021 meta-analysis of six RCTs (6930 patients) and 16 observational studies (183,546 patients) revealed that PPIs significantly reduced the risk of GI bleeding, and data from

Table 1 Increased risk of major adverse cardiac events (MACE) was similar with omeprazole, esomeprazole, lansoprazole, and pantoprazole but not with rabeprazole [28]

PPI	OR	Risk of MACE
Pantoprazole	1.52	Yes
Omeprazole	1.40	Yes
Lansoprazole	1.51	Yes
Esomeprazole	1.59	Yes
Rabeprazole	1.03	No

PPI proton pump inhibitors, *OR* odds ratio

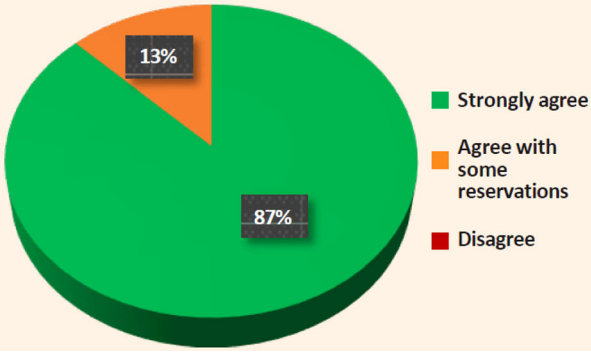

Fig. 14 Rabeprazole may be safer in terms of MACE risk than other PPIs when given along with clopidogrel. The figure shows that when concomitant use of a PPI and clopidogrel is warranted, rabeprazole may be safer than other PPIs in terms of MACE risk. The consensus level among participants was 100%, with 87% strongly agreeing and 13% agreeing with some reservations. *MACE* major adverse cardiovascular events, *PPI* proton pump inhibitor

observational studies showed that rabeprazole is not associated with any MACE [46]. Thus, rabeprazole does not interfere with the antiplatelet efficacy of clopidogrel and can be considered as a safer option than other PPIs [46–48] (Fig. 14).

Statement 14: It Is Safe to Use Newer Antiplatelet Drugs Along with PPIs

Review of the Literature

Unlike clopidogrel, newer anticoagulants like prasugrel and ticagrelor are less dependent on

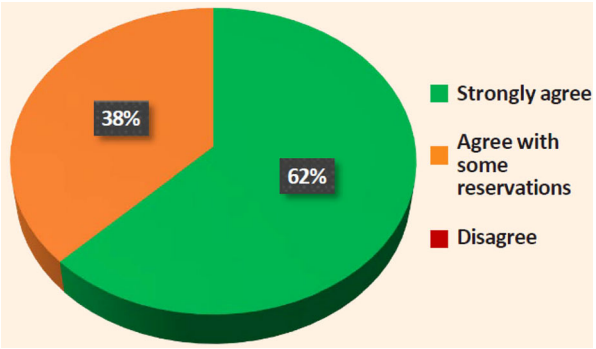

Fig. 15 Safety of concomitant use of newer antiplatelet drugs and PPI. The figure demonstrates that newer antiplatelet drugs can be used along with PPIs. The consensus level among participants was 100%, with 62% strongly agreeing and 38% agreeing with some reservations. *PPI* proton pump inhibitor

or are independent of CYP2C19 for bioactivation. Post hoc analysis of the PRINCIPLE-TIMI 44 and TRITON-TIMI 38 trials revealed that PPIs do not reduce the antiplatelet effect of prasugrel.

Further, ticagrelor is not a prodrug and it does not require the CYP system for its action; therefore, the efficacy of ticagrelor is not influenced by PPI co-prescription. Post hoc analysis of the PLATO (PLATelet inhibition and patient Outcomes) trial also suggests that the antiplatelet effect of these agents is less influenced by concomitant PPI use [47, 48] (Fig. 15). However, research data are not sufficient, and further studies are needed to explore this association or lack of it.

Nevertheless, PPIs should be prescribed judiciously in patients who are at increased risk of adverse GI events or who have a history of GI bleeding, because long-term unwarranted use may have adverse implications [49].

CONCLUSION

Following the process of discussion and voting by the expert panel, the interpretation of the results obtained indicates the need to review the prescribing strategy in the context of polypharmacy and select optimal candidates for prophylactic PPI therapy. In the management of

such patients, PPIs with minimal affinity for the CYP450 enzyme system and favorable interaction profile with other drugs should be preferred, and rabeprazole seems to be the most compatible PPI in CV co-therapy. Furthermore, unsupervised long-term consumption of PPIs outside the prescribed dosage regimen should be avoided, and the DDI profile should be considered to achieve optimal patient outcomes.

ACKNOWLEDGEMENTS

Springer Healthcare is not responsible for the validity of guidelines it publishes.

Medical Writing/Editorial Assistance. The authors thank Dr. Shipra Verma and Ajay Jha from Springer Nature India Pvt. Ltd., for medical writing support funded by Dr. Reddy's Laboratories, Hyderabad, India.

Authorship. Jamshed Dalal, Anjan Lal Dutta, Jagdish Hiremath, Shamanna Seshadri Iyengar, Jagadish Chander Mohan, Abraham Ooman, Bhabadev Goswami, and Kotacherry Thrivikrama Shenoy fulfill the criteria set by the International Committee of Medical Journal Editors (ICMJE) for authorship, take responsibility for the integrity of the work, and have provided their consent for the publication of this version.

Author Contributions. Jamshed Dalal, Anjan Lal Dutta, Jagdish Hiremath, Shamanna Seshadri Iyengar, Jagadish Chander Mohan, Abraham Ooman, Bhabadev Goswami, and Kotacherry Thrivikrama Shenoy were involved in drafting the article and revised it critically for important intellectual content. All authors read and approved the final manuscript. The authors acknowledge all the doctors who actively participated in the Advisory Board meetings and their insights were helpful in developing the final consensus statements and manuscript.

Funding. The advisory board meetings were conducted by Dr. Reddy's Laboratories, Hyderabad, India. The journal's Rapid Service Fee was supported by Dr. Reddy's Laboratories, Hyderabad, India.

Data Availability. Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Jamshed Dalal, Anjan Lal Dutta, Jagdish Hiremath, Shamanna Seshadri Iyengar, Jagadish Chander Mohan, Abraham Ooman, Bhabadev Goswami, and Kotacherry Thrivikrama Shenoy have nothing to disclose.

Ethical Approval. This article does not contain any new studies with human participants or animals performed by any of the authors.

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